

Pediatric Rhabdomyolysis

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Practice Gaps

Rhabdomyolysis is often encountered in the inpatient pediatric setting. Guidelines for managing pediatric rhabdomyolysis currently do not exist, but this article aims to review the available literature and give clinicians a general approach to aid in management.

Objectives

 After completing this article, readers should be able to:

1. Recognize the signs and symptoms of pediatric rhabdomyolysis.
2. Understand the pathophysiology of rhabdomyolysis.
3. Identify and prioritize causes of pediatric rhabdomyolysis to tailor history taking, diagnostic evaluation, and management.
4. Acutely manage pediatric rhabdomyolysis and recognize potential complications that may arise.
5. Develop a follow-up plan for individuals admitted to the hospital with rhabdomyolysis, including those with recurrent episodes.
6. Identify ways in which rhabdomyolysis can be prevented.

Abstract

Pediatric rhabdomyolysis is a common diagnosis that pediatricians need to be able to recognize because prompt treatment can prevent potential complications, such as acute kidney injury. The triggers for rhabdomyolysis are extensive, with viruses being the most common cause in pediatric patients. The pathophysiology behind rhabdomyolysis is complex and still being researched, but having a firm understanding of the cascade that results when muscle injury occurs is essential for proper management. Guidelines for managing pediatric rhabdomyolysis currently do not exist, but this article aims to review the available literature and give clinicians a general approach to aid in history taking, physical examination, diagnosis, acute management, follow-up, and prevention.

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ABBREVIATIONS

AKI acute kidney injury
ATP adenosine triphosphate
CK creatine kinase
IV intravenous

INTRODUCTION

Rhabdomyolysis in a broad sense is defined by the release of intracellular contents into the circulation after skeletal muscle damage that leads to systemic effects, including, most notably, acute kidney injury (AKI). (1) Consensus criteria are lacking, but based on a recent adult literature review, the most-used strict definition of rhabdomyolysis is a serum creatine kinase (CK) level greater than 5 times the upper limit of normal, or greater than 1,000 U/L ($>16.70 \mu\text{kat/L}$), with the pediatric literature often using the same definition. (2)(3) This laboratory finding is often coupled with the findings of myalgias, weakness, and pigmenturia. (2) This differs from myositis, in which there is muscle inflammation but the cell wall remains intact so there is no or minimal intracellular contents leaked into the circulation and the serum CK level is much lower than 1,000 U/L ($16.70 \mu\text{kat/L}$) or is normal. The triggers for this process are numerous and include infections, excessive muscle use, trauma, drugs, metabolic conditions, and myopathies. (4) The exact incidence of pediatric rhabdomyolysis is unknown, but 1 study has reported an incidence of 4 cases of rhabdomyolysis per 1,500 pediatric neurology consults in a large tertiary children's hospital over a 3-year period. (5) In addition, there are 25,000 pediatric and adult cases reported annually in the United States, with many mild cases likely going unrecognized. (3) Rhabdomyolysis is a relatively common diagnosis that most pediatricians will encounter, and, as such, they should have a firm understanding of this disease process. In particular there is a broad spectrum of severity and causality that needs to be appreciated to individualize care.

PATHOPHYSIOLOGY

The pathophysiology of rhabdomyolysis is complex but essential for understanding the clinical manifestations of the disease process. Understanding can be simplified by dividing the course into 2 broad categories: cell death and the release of contents that occurs after cell death.

Cell Death

Muscle injury can occur via either an insult to the cell's membrane or cellular energy depletion. Both insults eventually lead to the path of cell death, but the paths they take to get there differ. (6)

When the membrane itself is directly injured, free extracellular ionized calcium can enter the cell. (2)

On the other hand, when cellular energy, or adenosine triphosphate (ATP), is depleted due to impaired production or consumption, the transmembrane $3\text{Na}^+/2\text{K}^+/\text{ATPase}$

pump no longer can function, resulting in sodium accumulation in the cell. (7) To compensate, the $2\text{Na}^+/\text{Ca}^{2+}$ exchanger is activated to pump excess sodium out of the cell. (2) As noted previously herein, we again have calcium entering the cell. The cell has a $\text{Ca}^{2+}/\text{ATPase}$ pump to eliminate this excess calcium but without ATP cannot do so. (2) Excess calcium also causes repeated skeletal muscle contraction, further depleting ATP stores. (3)

Normally, intracellular sodium and calcium levels are kept low and the potassium level is kept high when cellular homeostasis is maintained with these pumps and channels. (8) In fact, the intracellular concentration of calcium is 10,000 times lower than the calcium concentration in the extracellular space. (1) However, with both paths we have an excess of intracellular calcium, which is catastrophic to cells. This imbalance activates proteases and phospholipases that destroy the cell membrane, allowing further accumulation of calcium. (2) This, in turn, destroys mitochondrial walls, leading to apoptosis and muscle cell necrosis. (2)

Release of Cellular Contents

Once muscle cell death has occurred, the release of intracellular contents into the extracellular space and circulation is responsible for the clinical manifestations we observe in rhabdomyolysis and set it apart from myositis. (6) All of the contents affect the surrounding tissues, including damage to local vasculature, edema, increased compartmental pressure, and ischemia. (1) Specific contents with their systemic effects and how they translate to the clinical findings we see are as follows:

1. Intracellular fluid is released into extracellular spaces, activating the renin-angiotensin-aldosterone system, decreasing renal blood flow and contributing to AKI. (2)
2. Myoglobin (an oxygen-carrying heme protein in muscle cells) is released, and when levels in the blood exceed the protein-binding capacity it precipitates in the glomerular filtrate. (9) Myoglobin goes on to cause AKI via 2 mechanisms. It is broken down into free iron, which reacts with hydrogen peroxide compounds to generate reactive oxygen species, which damage renal tubules. (2)(10) It also directly reacts with the lipid membrane components of the kidney to cause further damage. (2)(10)
3. Uric acid (a purine metabolite) is released from nucleosides and forms crystal deposits in an acidic environment, causing tubular destruction and AKI. (2)(7)(10)
4. Excess potassium, calcium, and phosphorous can lead to a variety of clinical manifestations. (2) Specifically, hyperkalemia can cause muscle weakness, paralysis, heart palpitations, syncope, and cardiac conduction disturbances (that evolve from peaked T waves to prolonged PR

interval to bundle branch block to ventricular fibrillation) that can ultimately lead to asystole if unrecognized. Hypercalcemia can cause nephrolithiasis, acute renal insufficiency, vomiting, constipation, muscle weakness, shortened QT interval, bradycardia, and hypertension.

Last, hyperphosphatemia can cause acute nephropathy. 5. Aldolase, CK, lactate dehydrogenase, and aspartate transaminase (muscle enzymes) are also leaked into circulation. (8)

HISTORY/CAUSES

There are a variety of acquired and inherited causes of skeletal cell injury that signal the process of rhabdomyolysis (Table 1). The most common cause in children is viruses, followed by inherited diseases and trauma/exercise. (3)(11)(12) Viruses and inherited diseases are a more common cause in the first decade of life, and trauma and medications peak as a cause in the second decade. (13)

Infections

Infections have been cited as the leading cause of pediatric rhabdomyolysis. In fact, viruses account for more than one-third of cases of pediatric rhabdomyolysis. (3) Influenza, Epstein-Barr virus, and cytomegalovirus have been repeatedly reported as responsible viruses. (3) Bacterial infections such as group A β -hemolytic streptococci and salmonella have been documented in the pediatric literature. (3) Last, protozoal infections such as malaria can be culprits as well. (3) Asking for travel history, vaccination status, and history of sick contacts can be helpful in revealing some of these causes.

Trauma/Exercise

Although trauma is the main cause of rhabdomyolysis in adults, it is less common in children. However, the incidence of exertional rhabdomyolysis in teenagers has been increasing. (14) Athletes and those in the military are populations to consider at risk for rhabdomyolysis due to excessive activity often after a period of being less active during the off season or before training camps. The presence of concomitant factors can put one at higher risk for exertional rhabdomyolysis, such as high humidity, sickle cell trait, electrolyte abnormalities, dehydration, high BMI, high altitude, or use of medications known to cause rhabdomyolysis. (3)(14) The type of exercise can also increase the risk of rhabdomyolysis. Eccentric contractions, which put tension on and elongate the muscle (such as when running downhill, resistance training, or weight lifting exercises when the muscles are extended), rather

TABLE 1. **Reported Causes of Pediatric Rhabdomyolysis**

ACQUIRED CAUSES
Viral infections
• Influenza A
• Influenza B
• Dengue
• Human herpesvirus 6
• Epstein-Barr virus
• Cytomegalovirus
• Respiratory syncytial virus
• Coxsackieviruses
Bacterial infections
• Salmonella
• Malaria
• <i>Brucella</i>
• <i>Mycoplasma pneumoniae</i>
• <i>Legionella</i>
• <i>Streptococcus pyogenes</i>
• <i>Staphylococcus aureus</i>
Muscle strain/excessive activity/trauma
• Strenuous or prolonged exercise
• Convulsive seizure
• Dystonic reactions
• Abrupt withdrawal of muscle-relaxing medication (baclofen)
• Heatstroke
• Hypothermia
• Crush injury
• Compartment syndrome
• Surgery
Medications
• Neuroleptics
• Statins
• Anesthesia agents causing malignant hyperthermia
• Isotretinoin
• Lithium
• Colchicine
• Corticosteroids
• Cyclosporine

Continued

TABLE 1. (Continued)

Illicit drugs
• 3,4-Methylenedioxy-methamphetamine
• Heroin
• Marijuana
• Cocaine
Toxins
• Ethanol
• Carbon monoxide
• Para-phenylenediamine (found in hair dye and henna)
• Multiple wasp or hornet stings
• Snake venom
Food/ingestions
• Quail eggs
• Mushrooms
• Licorice
Metabolic
• Nonketotic hyperosmolar coma
• Thyroid disease
• Diabetic ketoacidosis
• Hypokalemia
• Hypophosphatemia
Inherited Disorders Predisposing to Rhabdomyolysis
Inborn errors of metabolism
• Fatty acid oxidation defects
◦ Carnitine palmitoyltransferase II deficiency
◦ Very long chain acyl-CoA dehydrogenase deficiency
◦ Mitochondrial trifunctional protein combined enzyme deficiency
• Muscle phosphatidic acid phosphatase deficiency (<i>LPIN1</i> gene mutation)
• Mitochondrial disorders
◦ MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) syndrome due to A3243G or A3260G mutation
◦ Cytochrome b oxidase deficiency
◦ Cytochrome c oxidase deficiency
• Glycogen storage diseases
◦ Myophosphorylase deficiency (McArdle disease)
◦ Phosphofructokinase deficiency (Tarui disease)
◦ Phosphorylase B kinase deficiency

Continued

TABLE 1. (Continued)

◦ Phosphorylase mutase deficiency
◦ Lactate dehydrogenase-A deficiency
◦ β -Enolase deficiency
◦ Glycogen synthase deficiency
Muscular dystrophies
• Duchenne and Becker
• FKRP-related
• Dysferlinopathy
• Sarcoglycanopathy
• Anoctamin 5
Congenital myopathies
• Ryanodine receptor 1-related myopathy
• Selenoprotein N-related myopathy
Inflammatory myopathies
• Sarcoidosis
• Polymyositis
• Dermatomyositis

than concentric contractions, or flexion of muscle, can predispose one to rhabdomyolysis. (3) Overemphasis on a single muscle group, not allowing recovery time between exercises, increasing weight amounts too quickly when weightlifting, and workouts after a practice or a game are other risk factors for developing rhabdomyolysis. (14) In addition, it has been postulated that some people are at higher risk for muscle breakdown in response to exercise than others due to genetic polymorphisms that have been described. (3)

Medications/Toxins/Ingestions

Medications are a much more common trigger in adults, and it is important to note that more than 200 medications have been cited to cause rhabdomyolysis. (3) The medications listed in Table 1 have been more commonly known to cause rhabdomyolysis and are medications more frequently used in the pediatric population. When obtaining a history of the patient it is important to think of these causes and tailor questions appropriately to try to unveil a trigger. A thorough social history should be obtained to screen for illicit drug use in adolescents. Known agents include alcohol (acute intoxication or withdrawal symptoms, including delirium tremens and seizures), cocaine,

heroin, marijuana, amphetamines, ecstasy, and lysergic acid diethyl-amide. (3)

Inherited Disorders

There are a variety of genetic causes for rhabdomyolysis, many being rare metabolic conditions as listed in Table 1, but they are important to consider when faced with a patient with recurrent rhabdomyolysis. Inherited disorders can be characterized by those of lipid metabolism, glycogen metabolism, mitochondrial function, muscular dystrophies, and other myopathies. Carnitine palmitoyltransferase II deficiency and McArdle disease (an autosomal recessive disorder caused by a mutation of the *PYGM* gene leading to myophosphorylase deficiency) are the most common inherited myopathies that cause recurrent rhabdomyolysis. (4)(15)(16)(17) It is important to obtain a thorough family history because many of these conditions are inherited. Differences in symptomatic presentation can help differentiate between these conditions and be suggestive of an underlying inherited cause.

SYMPTOMATIC PRESENTATION

The classic acute presentation of rhabdomyolysis includes myalgias, muscle weakness, and tea-colored urine. Not many other conditions present with this triad, but be mindful of other diagnoses if all 3 symptoms are not present. Myalgias are the most common presenting symptom and often the only symptom in pediatric patients, so index of suspicion based on history and severity of myalgias needs to be high. (12)

Fever should make you think of an infectious cause or malignant hyperthermia if the patient had exposure to anesthetics recently. If an infectious cause was the trigger, symptoms such as a sore throat or upper respiratory symptoms may be present. Patients may also present with oliguria or anuria if AKI is present. (2)

It is important to take a history of symptoms associated with exercise and fasting because this can often help uncover an underlying inherited disorder. In general, one should consider an underlying neuromuscular condition if the symptoms exceed the possible cause. Patients reporting myalgias and cramps within minutes of moderate-to-high-intensity activity, a phenomenon known as “out of wind,” should be screened for glycogen storage diseases. (4) Furthermore, a history of resolution of symptoms after resting for approximately 6 to 10 minutes (a phenomenon known as “second wind”) is suspicious for McArdle disease. (4) A history of stiffness or weakness after low-intensity but prolonged activity lasting greater than 30 minutes or

fever/heat-triggered symptoms is suspicious for a fatty acid oxidation defect. (4) Last, symptoms of rhabdomyolysis after fasting are suspicious for a mitochondrial disorder. (4)

EXAMINATION FINDINGS

When patients present with signs and symptoms suspicious for rhabdomyolysis, it is important to first assess the patient clinically, including completing a full examination and assessment of vital signs to ensure that no interventions are needed emergently. A thorough neuromuscular examination to assess for extremity muscle weakness, tenderness, and abnormal gait due to pain should be performed. Because compartment syndrome is a known complication of rhabdomyolysis, one should assess extremities for pallor, diminished pulses, tenderness, and paresthesia.

Physical examination can also determine underlying causes for rhabdomyolysis. Mental status and pupil size should be assessed because this can provide insight into drug or toxin exposure. Ptosis and ophthalmoplegia can be seen in some mitochondrial disorders and muscular dystrophies. (4) Hepatosplenomegaly can be seen in Epstein-Barr virus, cytomegalovirus, and glycogen storage diseases. Proximal muscle weakness may indicate a muscular dystrophy as well. (4) Nasal congestion, rashes, lymphadenopathy, and pharyngitis can reveal a possible infectious cause. A thorough skin examination for signs of injury, drug use, bites, and stings should also be performed.

DIAGNOSTIC STUDIES

The diagnosis of rhabdomyolysis needs to be made via laboratory testing as soon as rhabdomyolysis is suspected. Children seen in the outpatient setting should be sent to the emergency department for laboratory testing. Once the diagnosis is confirmed, if not apparent from history, more specific investigative studies to look for an underlying cause should be initiated.

Initial Studies

When rhabdomyolysis is suspected based on history and examination findings, initial studies that need to be sent include a serum CK level, comprehensive metabolic panel, microscopic urinalysis, and complete blood cell count to evaluate for electrolyte abnormalities, kidney function, hydration status, and leukocytosis suggestive of infection. Urine and serum myoglobin can also be sent, but limitations and disadvantages of these studies are discussed later herein. If electrolyte abnormalities are present, an electrocardiogram should be obtained and cardiac monitoring with telemetry considered depending on severity.

Although there are no set criteria for the diagnosis of rhabdomyolysis, an elevation in CK level is used for diagnosis by clinicians because it is the most sensitive enzyme marker for muscle breakdown. (3) There is no consensus on the cutoff value in pediatric or adult patients, but most consider more than 5 times the upper limit of normal (or $\sim 1,000$ U/L [~ 16.70 $\mu\text{kat/L}$]) diagnostic. The CK level rises 12 hours after the initial insult, peaks at approximately 2 to 5 days, and returns to normal in most patients 6 to 10 days later. (2)

The myoglobin level, which rises before the CK level, can be measured in serum or urine to confirm the diagnosis. (2) However, the drawbacks include a high false-negative rate because it has a half-life of only 1 to 3 hours, and results are not reported in a timely manner. (18) Dipstick urinalysis positive for blood and negative for red blood cells is suspicious for myoglobinuria and also supports the diagnosis. Myoglobinuria causes color change in the urine when levels exceed $250,000$ $\mu\text{g/L}$ ($14,535$ nmol/L), at which point more than 100 g of muscle tissue has been destroyed. (19)

The incidence of AKI may be lower in children than in adults, with the largest pediatric case series ($N = 191$) reporting an incidence of approximately 5%. (13) Higher initial CK levels have been shown to be a risk factor for AKI in pediatric patients. (13)(20) However, larger adult studies have shown that initial CK and myoglobin levels are not good predictors of AKI or mortality. (2) A validated tool for predicting AKI and mortality in adult patients with rhabdomyolysis takes into account age, sex, etiology, and initial levels of creatinine, calcium, phosphate, and serum bicarbonate. (21)

Disseminated intravascular coagulation can be a late complication of rhabdomyolysis, so checking coagulation studies should be considered in those with a delayed diagnosis, with thrombocytopenia, or who are ill-appearing. (3)

Cause-Related Studies

Evaluation for a single initial episode of rhabdomyolysis is based on clinical history and examination findings. For example, when an infectious etiology is suspected, testing directed at specific viruses or cultures for bacteria can be sent based on clinical presentation. In addition, if a medication or toxin is suspected, serum drug levels and/or a urine toxicology screen can be obtained. If history strongly suggests or diagnostic evaluation confirms a cause for rhabdomyolysis, no further evaluation is necessary.

However, when an initial episode cannot be attributed to infection, exercise, medications, or toxins based on history, physical examination, or diagnostic studies, further evaluation is necessary to look into other causes. In addition,

those with an initial episode and a personal history of myalgias or a family history of a myopathy should also undergo additional investigations. Last, those with more than 1 episode of rhabdomyolysis also deserve further diagnostic studies.

In the acute setting, when an inborn error of metabolism is suspected, diagnostic testing should target the specific disorder suspected. For patients with concern for a glycogen storage disease, levels of liver enzymes, bilirubin, lactate dehydrogenase, and uric acid as well as fasting glucose, ammonia, lactate, and lipid panel can be performed as screening tests. (4) Specific genetic testing can be considered as well, such as *PYGM* sequencing for McArdle disease. (4) When fatty acid oxidation defects are suspected, levels of liver enzymes, fasting glucose, ammonia, lactate, ketones, total and free carnitine and acylcarnitines, free fatty acids, urine organic and amino acids, and urine acylglycines can be determined. (4) Specific gene testing can again be performed as well. (4) When mitochondrial disorders are suspected, serum lactate, pyruvate, and urine organic and amino acids can be sent for laboratory testing. (4) When it is hard to decipher which inborn error of metabolism could be causing symptoms, all of the above can be performed. A pediatric neurologist and a geneticist are often helpful in guiding this initial evaluation as well.

Other tests can be helpful at arriving at a cause but are usually requested by a pediatric neurologist in the outpatient setting on follow-up. Muscle biopsy will show only nonspecific findings of muscle injury but will not assist in determining the underlying etiology until 6 weeks to 3 months after symptom resolution. (4) At that time specific enzyme assays can be performed. (4) Findings from electromyography and muscle magnetic resonance imaging can be suggestive of an underlying myopathy when abnormal once patients are asymptomatic, but these findings are very nonspecific and often are only suggestive of a myopathy or muscle inflammation. (4) In patients with recurrent exercise-induced rhabdomyolysis, a forearm exercise test can be performed to screen for a metabolic myopathy by looking at lactic acid and ammonia levels before and after sphygmomanometer cuff placement. (3)

ACUTE MANAGEMENT

The Figure gives a general algorithm for the management of patients with rhabdomyolysis. When patients are diagnosed as having rhabdomyolysis, they need to be admitted to the hospital for IV fluids, close clinical monitoring, possible consults, and frequent laboratory tests. Admission to the ICU may be required for those with severe

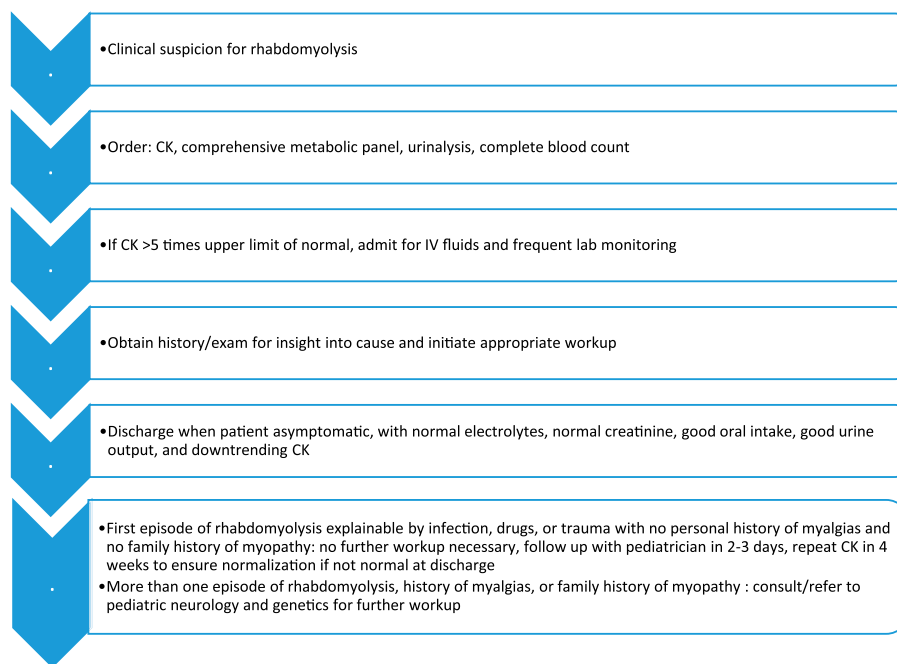


Figure. Management algorithm for pediatric rhabdomyolysis. CK=creatinine kinase, IV=intravenous.

electrolyte abnormalities, arrhythmias, or AKI requiring dialysis.

The overall goal in the treatment of rhabdomyolysis is to preserve renal function and prevent AKI. There is consensus and evidence that this is achieved via administration of IV fluids. (3) However, there is much variation in the type, rate, and duration reported, without any set guidelines for adult or pediatric patients. (14)(22)

Normal saline is the most commonly used fluid choice. (3) The addition of sodium bicarbonate to IV fluids or the use of lactated Ringer solution has been considered in the acute management of rhabdomyolysis because animal studies have shown that alkalization of urine decreases cast formation. (3) Studies comparing the use of lactated Ringer solution and normal saline showed no difference in the incidence of AKI or the rate of reduction of the CK level. (2) Studies comparing outcomes of those who received normal saline versus IV fluid with sodium bicarbonate are lacking in adult and pediatric patients. (22) Many experts recommend adding only sodium bicarbonate to IV fluids if the patient is acidotic. (22)

Rate of IV fluid resuscitation practices vary greatly. In adults, a rate of 1.5 L per hour initially is suggested. (3) Some experts recommend using a urine output goal of at least 200 mL per hour for the first 24 hours and tailoring IV fluid rates accordingly for adult patients. (3)(22) In pediatric patients, many clinicians will give an initial 20-mL/kg bolus and then start twice the maintenance rate IV fluids. Additional

boluses can be given and the IV fluid rate can be adjusted based on urine output, serum CK level, and net fluid balance. There are no urine output goals for pediatric patients published, but given that the recommended urine output is approximately 3 to 4 times normal urine output for an adult, one could hypothesize for children a targeted urine output to be 3 to 4 times the normal urine output for pediatric patients, or approximately 3 to 4 mL/kg per hour. It has been shown that rapid initiation of IV fluids decreases the risk of acute renal failure, specifically if administered within the first 6 hours after muscle injury. (22)

The addition of mannitol has been postulated to assist in diuresis and, hence, prevent AKI. However, a systematic review of adult patients by Scharman and Troutman (22) found no benefit over normal saline fluid but did state that it would be reasonable to add if a urine output of 300 mL per hour is not achievable with IV fluid therapy alone, based on expert opinion.

In general, more randomized controlled studies need to be performed comparing fluid rates, use of mannitol versus normal saline alone, and use of sodium bicarbonate versus normal saline alone. Studies are lacking in both the adult and pediatric literature.

CK, electrolyte, and creatinine levels should be measured at least twice daily until the CK level is downtrending, electrolyte levels have normalized, and AKI has resolved. However, the frequency of laboratory testing should vary based on the severity of the CK level, rate of rise of the CK

level, presence of AKI, timing of presentation, and presence of electrolyte abnormalities. This requires some clinical judgment to ensure that complications are not missed. One can approximate when the CK level should peak based on its half-life and when the insult occurred. If the CK level continues to climb past the approximated peak, one should consider ongoing insult. If the CK level is not normalizing in an expected period, one should consider this to be the patient's baseline, which would be concerning for an underlying myopathy.

In addition, nephrotoxic medications such as nonsteroidal anti-inflammatory drugs should be avoided. Drugs or medications that may have caused rhabdomyolysis should be discontinued. Electrolytes should be replaced as needed. In patients who develop disseminated intravascular coagulation, fresh frozen plasma can be given.

Pediatric neurology and genetics consults should be considered when there is suspicion for an underlying myopathy based on history or physical examination findings, especially for patients with more than 1 episode of rhabdomyolysis. An initial evaluation can begin in the hospital, but often a diagnosis is not made until after discharge given that many of these tests take days to weeks to result. A pediatric nephrology consult should be considered when AKI is present or the patient has poor urine output despite aggressive hydration. A retrospective study performed at a tertiary care center's ICU reported that 29 of 182 patients (16%) admitted to their PICU with rhabdomyolysis required renal replacement therapy. (11) A pediatric surgeon should be consulted if there is concern for compartment syndrome.

Degree of elevation of the CK level has not been shown to be predictive of mortality, and chronic kidney disease is a rare complication of rhabdomyolysis in children requiring intensive care. (11) Reported mortality rates in children are 7% to 10%, but all died secondary to their underlying etiology and not rhabdomyolysis. (8)

There is no consensus on discharge criteria, but based on expert opinion, patients should be asymptomatic (or greatly improved), with normal electrolyte levels, normal creatinine levels, good oral intake, good urine output, and downtrending serum CK levels. (23) It is also reasonable to ensure that the serum CK level is less than 5,000 U/L ($<83.50 \mu\text{kat/L}$) before discharge because this is the lowest abnormal level associated with renal failure in a large study of 2,083 adult trauma ICU patients. (24)

FOLLOW-UP

In patients with their first episode of rhabdomyolysis explainable by infection, drugs, or trauma with no personal

history of myalgias and no family history of myopathy, no further evaluation is necessary. (8) These patients should follow up with their pediatrician 2 to 3 days after discharge to ensure continued clinical improvement. If the CK level is still elevated at the time of discharge, it is reasonable to repeat a serum CK level in 4 weeks to ensure normalization of serum CK levels.

Although recurrent rhabdomyolysis is not common (studies in pediatric patients have reported an incidence of ~5%–8%), one should assume that when there is recurrence, the patient has an underlying myopathy until proven otherwise. (25) Patients with more than 1 episode of rhabdomyolysis, a history of myalgias, or a positive family history of myopathy should undergo initial evaluation as stated previously herein in the inpatient setting in conjunction with a pediatric neurologist and geneticist. They should also follow up in the outpatient setting because many tests cannot be performed in the acute setting and/or may take weeks for a final result.

For athletes, return to play is an important consideration, and there currently are no guidelines for when return to play is appropriate. Cleary et al (26) suggest that return to play is safe when the athlete is afebrile and asymptomatic, the CK level has returned to normal, and myoglobin is no longer present in the serum and urine. When athletes do return to play, types of exercise that are known to cause rhabdomyolysis, such as eccentric exercise, should be avoided initially, with a gradual increase in activity. (26) Aquatics has been suggested as an optimal means of return to activity, providing strengthening with less muscle strain and exposure to heat. (26)

PREVENTION

Prevention of rhabdomyolysis largely depends on the underlying cause. In children, infectious causes are hard to avoid, but certainly emphasizing the importance of vaccinations and good hand hygiene is always important.

To prevent exertional rhabdomyolysis, athletes and those participating in any exercise need to be aware of the importance of gradually easing into exercise, especially after a period of inactivity or less activity. Avoidance of confounding factors such as heat and dehydration during exercise should be stressed as well. Coaches and players need to be educated and aware of the risk factors for developing rhabdomyolysis. The National Collegiate Athletic Association established a guideline in 2005, updated in 2013, that stresses following a 5-day heat acclimation period to prevent heat-related illness. Other schools have adopted a similar protocol. (27) Pediatricians

during sports physicals can also be a source of education to athletes.

Prevention of rhabdomyolysis in those with underlying myopathies involves treating the individual cause such as avoidance of fasting, dietary modifications, and instructions on hydration during times of stress, intense activity, and illness.

Patients taking medications known to potentially cause rhabdomyolysis should be counseled at medication initiation regarding presenting signs and symptoms and to avoid risk factors associated with exertional rhabdomyolysis. In addition, patients undergoing anesthesia should be questioned regarding personal or family history of anesthesia reactions before administration.

Summary

- Infections are the leading cause of pediatric rhabdomyolysis, but other causes need to be considered when patients do not present with findings from history, physical examination, or studies suggestive of infection.
- Based on expert opinion, a serum creatine kinase (CK) level greater than 5 times the upper limit of normal is used for the diagnosis of pediatric rhabdomyolysis. (3)
- Based on observational studies, intravenous (IV) fluids are the mainstay of treatment for rhabdomyolysis, with greatest prevention of acute kidney injury when initiated within 6 hours of insult. (3)(22)
- Based on observational studies and expert opinion, IV normal saline at a rate that provides urine output of at least 200 mL per hour is recommended for acute management of rhabdomyolysis. (3) For smaller pediatric patients, we can assume that a similar output of 3 to 4 mL/kg per hour would be an appropriate target, but more studies need to be performed to support this. There is a lack of randomized controlled trials and no observational study evidence to support routine use of mannitol and sodium bicarbonate in patients with rhabdomyolysis. (3)(22)
- Based on expert opinion, discharge can be considered once patients are asymptomatic (or greatly improved), with normal serum electrolyte levels, a normal serum creatinine level, good oral intake, good urine output, and downtrending serum CK levels (some clinicians use 5,000 U/L [83.50 μ kat/L] as a goal given that this is the lowest reported serum CK level associated with acute kidney injury). (23)(24)
- Based on expert opinion, those with a single episode explained by an infection, medication, or trauma require no additional evaluation. However, those with recurrent episodes of rhabdomyolysis, a personal history of myalgias, or a family history of a myopathy warrant further metabolic and genetic testing. (3)

- Prevention of rhabdomyolysis largely depends on the underlying cause and requires education of clinicians on the risk factors for the disease and education of patients who are at risk for rhabdomyolysis. Populations at risk include athletes and those taking certain medications. Handwashing and vaccination are important for preventing the spread of infection, which is the most common cause of rhabdomyolysis in pediatric patients.

POTENTIAL QI PROJECTS

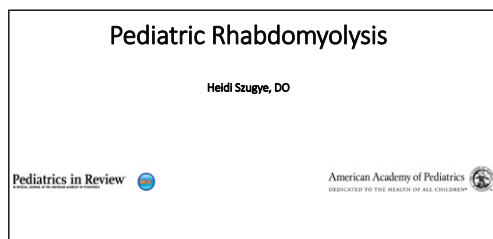
1. Improve outcomes of cases of rhabdomyolysis by looking at time to treatment and residual effects on kidney function after treatment.
2. Decrease the incidence of rhabdomyolysis or increase awareness and understanding by educating coaches or incorporating education into sports physical examination visits.
3. Improve detection of patients with a chronic underlying cause for rhabdomyolysis by ensuring that all patients admitted with rhabdomyolysis have a documented cause or a plan for investigating cause if not documented.

Readings, Suggested Readings

The Sydney Children's Hospital Network. Practice guideline: acute rhabdomyolysis—investigation and management. Available at: http://www.schn.health.nsw.gov.au/_policies/pdf/2008-8005.pdf. Accessed September 8, 2018

The National Collegiate Athletic Association. 2014-2015 NCAA Sports Medicine Handbook: guideline 2T: exertional rhabdomyolysis. Available at: <https://www.ncaapublications.com/productdownloads/MD15.pdf#page=99>. Accessed December 18, 2018

To view teaching slides that accompany this article, visit <http://pedsinreview.aappublications.org/content/41/6/265.supplemental>.



References for this article are at <http://pedsinreview.aappublications.org/content/41/6/265>.

PIR Quiz

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1. A 15-year-old boy presents to the emergency department with new-onset tea-colored urine and right calf pain the morning after football practice. He reports that he has been vomiting all morning and that his muscles are weak. On physical examination his heart rate is 50 beats/min and his blood pressure is 150/100 mm Hg. He was diagnosed as having suspected rhabdomyolysis. Which of the following laboratory abnormalities is most likely to be seen in this patient and to account for his hypertension?
 - A. Anemia.
 - B. Hypercalcemia.
 - C. Hypermagnesemia.
 - D. Hypokalemia.
 - E. Hypophosphatemia.
2. A 16-year-old girl is brought to the emergency department by emergency medical services after her mom found her "not acting right." She is breathing at a rate of 8 breaths/min and her heart rate is 60 beats/min. Her pupils are pinpoint and she is sleepy. The patient is admitted for observation. Over the next 12 hours she starts having emesis and cold shivers, but she does not have a fever. Her creatine kinase (CK) level is 7,000 U/L (116.90 μ kat/L). Which of the following is the most likely cause of all of her symptoms?
 - A. Autoimmune disorder.
 - B. Cocaine use.
 - C. Genetic disorder.
 - D. Opioid use.
 - E. Viral illness.
3. A 3-year-old girl is brought to your office by her mother with the concern of exercise intolerance. She started playing soccer at preschool and had to sit down after approximately 5 minutes of activity as she was complaining of cramping and muscle pain. Mom says that this happens when she runs in the backyard, but not this bad. She remembers that her cousin had something similar, but the family moved away when he was young and she has not seen them in years. Evaluation for which of the following disorders is most likely to diagnose the cause of her symptoms?
 - A. Congenital myopathy.
 - B. Fatty acid oxidation defect.
 - C. Glycogen storage disease.
 - D. Inflammatory myopathy.
 - E. Mitochondrial disorder.
4. A 6-year-old boy is brought to the clinic for follow-up. He was seen in the emergency department the previous day and was discharged with the diagnosis of influenza A. He is still having fevers and now has new-onset arm and leg pains bilaterally. He has not been having good oral intake, and now his urine output is decreased. Serum laboratory studies are ordered and showed a CK level of 5,000 U/L (83.50 μ kat/L). He is admitted to the hospital for intravenous (IV) hydration and is started on 1.5 \times maintenance IV fluids. A recheck of the CK level is ordered for the following day. The following morning during rounds mom is worried because the repeated CK level is now 20,000 U/L (334.00 μ kat/L). The clinical team increases the IV fluid rate to 2 \times maintenance. In explaining the clinical course to mom, which of the following approaches is the most appropriate for the clinical team to take at this point?

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- A. Ask mom if he has been walking around the hospital because this is the most likely reason for the CK level increase.
 - B. Because of lack of response to fluids, an evaluation for genetic causes of rhabdomyolysis is indicated at this point.
 - C. Explain to mom that a muscle biopsy is indicated at this time to rule out other diagnoses.
 - D. Explain to mom that this is not concerning because it is most likely a laboratory error.
 - E. This is not unexpected because it takes typically 2 to 5 days for the CK level to peak.
5. The patient in the vignette in question 4 was sent home 3 days later with a CK level of 5,000 U/L (83.50 μ kat/L). He returns to the office 48 hours later for follow-up. A repeated CK level at this time is 3,500 U/L (58.45 μ kat/L). The mother wants to know when he can go back to playing tennis with his best friend. Which of the following is the best follow-up plan for this patient?
- A. Avoid playing sports because he is more likely to get rhabdomyolysis again.
 - B. Order genetic testing; if the results are negative he can restart sports.
 - C. Recheck the CK level in 4 weeks; if normal at that time he can gradually restart sports.
 - D. Return to full sports participation now and premedicate with nonsteroidal anti-inflammatory drugs before exercise for the next 4 weeks.
 - E. Return to full sports participation because the CK level is going down; no repeated CK level is needed.

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